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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/565,100	08/29/2006	Nicola Frances Bateman	056291-5230	6134

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MORGAN LEWIS & BOCKIUS LLP
1111 PENNSYLVANIA AVENUE NW
WASHINGTON, DC 20004

EXAMINER	
DICKINSON, PAUL W	
ART UNIT	**PAPER NUMBER**
1618	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/545,100	HU ET AL.	
	Examiner	Art Unit	
	PAUL DICKINSON	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) *3,5,7 and 17-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,6 and 8-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 January 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/4/2006 and 11/3/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group I, Claims 1-16, in the reply filed on 1/7/2008 is acknowledged. Applicant's election without traverse of the following is also acknowledged: Fumaric acid as the water-soluble acid and hydroxypropyl methylcellulose as the species of ether.

Claims 1-19 are pending. Claims 3, 5, 7 and 17-19 are directed to a nonelected species and are hereby withdrawn. Claims 1-2, 4, 6 and 8-16 are currently under consideration.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-2, 4, 6 and 8-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 5770559 (hereafter '559) in view of WO 2003072139 (hereafter '139; document provided by Applicant) in further view of US 20040109890 (hereafter '890). '559 discloses the instantly claimed compound, 4-(3'-chloro-4'fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)quinazoline (hereafter "the Agent") (see entire document, specifically col 8, lines 61-64; Example 1). '559 further discloses that the compounds exemplified in the reference can be formulated into pharmaceutical compositions in association with a pharmaceutically acceptable diluent or carrier (col 13, line 65 to col 14, line 3; Claim 17). The composition may be in a form suitable for oral administration, for example as a tablet or capsule (col 13, lines 4-5). The instant claims differ from '559 in that they recite specific excipients and proportions of excipients to active agents.

'139 discloses the instantly claimed compound (i.e. "the Agent") possesses anti-proliferative activity such as anti-cancer activity (see p 1, lines 7-15). '139 further

discloses that the solubility of the Agent is highly dependent upon pH. For example, the free-base form of the Agent is soluble at pH 1 (acidic media) but is practically insoluble above pH 7 (neutral to alkaline media), with the solubility dropping sharply between pH 4 and pH 6 (see p 1, line 22 to p 2, line 2). '139 further discloses that the rate at which the Agent is precipitated from solution when the pH of the solution increases from a pH similar to that of the stomach to a pH similar that found in the upper GI tract is significantly reduced when the Agent is formulated or administered together with certain excipients, including water-soluble cellulose ethers, such as hydroxypropyl methylcellulose (see p 3, line 11-18; p 4, line 30 to p 5, line 15; p 8, lines 8-9).

'890 discloses intraorally rapidly disintegrating tablets which disintegrate in the oral cavity rapidly without presenting unpleasant taste and can be quickly absorbed in the digestive tract (see entire document, specifically abstract, ¶ 1, 13-32). The disclosed tablets contain a drug that is sparingly water-soluble under neutral or alkaline conditions but highly water-soluble under acidic conditions. The rapidly disintegrating tablets comprise the following ingredients:

i) a medicinal substance being hardly water-soluble under alkaline or a neutral condition and being highly water-soluble under acidic conditions yet presenting an unpleasant taste under acidic conditions;

ii) a water-soluble acidic substance

iii) a water-soluble binding agent being soluble in alcoholic solvent and

iv) a water-soluble saccharide (see ¶ 14-10).

Fumaric acid and malic acid are preferred water-soluble acidic substances (see ¶ 26). Cellulose derivatives such as hydroxypropyl cellulose are preferred and exemplified water-soluble binding agents (see ¶ 27; Examples 1-2). Hydroxypropyl methylcellulose is also listed as a cellulose derivative (see ¶ 29). In the exemplified tablets, cellulose ethers are used as a binding agent and also as a component in a coating (see Examples 1-2). The molar ratio of the medicinal substance to fumaric acid is 1:1 (calculated from 40 grams medicinal substance = 0.1 mol, using MW = 482; 12 grams fumaric acid = 0.1 mol, using MW = 116) (see Examples 1-2). In the exemplified tablets, the weight ratio of the medicinal substance to hydroxypropyl cellulose is 11:1 (calculated from 50 grams medicinal substance to 4.4 grams hydroxypropyl cellulose). The disclosed tablets increase the solubility of the medicinal substance and improve the overall dissolution profile of the drug (see ¶ 7, 24, 195).

One of ordinary skill in the art would be motivated to combine the disclosures of '559, '139 and '890 to afford the instant invention with a reasonable expectation of success. Specifically, in an effort to discover improved oral formulations of the Agent, one would be motivated to prepare a pharmaceutical composition comprising the Agent, fumaric acid, and hydroxypropyl methylcellulose. '559 discloses that the Agent may be formulated into pharmaceutical compositions in association with a pharmaceutically acceptable diluent or carrier and that the composition may be in a form suitable for oral administration, for example as a tablet or capsule. '139 discloses that the solubility of the Agent is highly dependent upon pH, being practically insoluble around or above pH 7 (neutral or alkaline conditions) but soluble at pH 1 (acidic conditions). One would

therefore be motivated to choose as the excipients a water-soluble acidic substance and a water-soluble binding agent, as these excipients are disclosed by '890 to be beneficial in orally delivering medicinal substances that are insoluble at neutral and alkaline pH, but soluble in acidic conditions. One would be motivated to choose fumaric acid as the water-soluble acidic substance, as it is disclosed for this purpose by '890. One would choose hydroxypropyl methylcellulose as the water-soluble binding agent. The motivation to do this stems from the fact that cellulose derivatives are disclosed by '890 as preferred water-soluble binding agents, and, according to the same reference, hydroxypropyl methylcellulose is encompassed by the term "cellulose derivative". Further motivation stems from the teaching of '139 that hydroxypopyl methylcellulose is a preferred excipient in formulations comprising the Agent due to their role in improving the solubility of the drug. One would be motivated to choose the form of a tablet or capsule formulation, as these forms are contemplated by '559, and the composition disclosed by '890 is in the form of a (rapidly disintegrating) tablet. The phrase "immediate release" in Instant Claims 1-2, 4, 6 and 8-16 is an intended use and is not given patentable weight. It is noted, however, that the formulation disclosed by '890 (rapidly disintegrating tablets) would be considered an immediate release formulation in light of the instant specification.

Instant Claim 14 is directed to a pharmaceutical composition comprising (i) from 10 to 60 parts of the Agent; (ii) from 2 to 70 parts of hydroxypropyl methylcellulose; and (iii) from 10 to 70 parts of fumaric acid, wherein all parts are by weight and the sum of the parts (i)+(ii)+(iii)=100; and wherein the molar ratio of Agent to fumaric acid is from

1:3 to 1:6. One would be motivated to choose these components as described above. With regard to the specific ratios of the components, it is the position of the examiner that such limitations do not impart patentability absent a showing of criticality. The prior art discloses compositions comprising the active agent and excipient of the recited claim. Applicant is reminded that where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. See *In re Aller*, 220 F.2d 454 105 USPQ 233,235 (CCPA 1955).

. Instant Claim 12 is directed to a composition wherein the molar ratio of Agent to acid is from 1:1 to 1:10. Instant Claim 13 is directed to a composition wherein the weight ratio of Agent to water-soluble cellulose ether is from 30:1 to 3:1. As argued above, it is the position of the examiner that the ratio limitations in these claims do not impart patentability absent a showing of criticality. It is noted, however, that one of ordinary skill in the art would reasonably choose values within the range disclosed by Instant Claim 12, because the molar ratio of medicinal substance to fumaric acid disclosed by '890 is 1:1. It is further noted that one of ordinary skill in the art would reasonably choose values within the range disclosed by Instant Claim 13, because the weight ratio of medicinal substance to hydroxypropyl cellulose (a water-soluble cellulose ether) disclosed by '890 is 11:1.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory

obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-2, 4, 6 and 8-16 are provisionally rejected on the ground of nonstatutory double patenting over claim 1-18 of copending Application No. 10505231. This is a provisional double patenting rejection since the conflicting claims have not yet been patented. Although the conflicting claims are not identical, they are not patentably distinct because both the copending claims and those of the instant invention are directed to a composition comprising the Agent and a water-soluble cellulose ether or an ester of a water-soluble cellulose ether. The claims differ in that the copending claims fail to disclose a composition comprising a water-soluble acid. However, a skilled practitioner in the art would be motivated to incorporate fumaric acid, a water-soluble acid, into the composition since the copending application discloses this component as an optional ingredient (see p 7, line 11).

Conclusion

No Claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to PAUL DICKINSON whose telephone number is (571)270-3499. The examiner can normally be reached on Mon-Thurs 9:00am-6:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Paul Dickinson
Examiner
AU 1618

February 9, 2008

MICHAEL G. HARTLEY
SUPERVISORY PATENT EXAMINER